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Epidemiology and outcome of Human Fusariosis

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1. Summary

Background: Fusarium is a mold mainly known as plant and animal pathogen. Recently, there has been an increasing number of reports about fusarium infection in humans, especially as opportunistic infection in immunocompromised patients with a significant morbitiy and mortality rate. The aim of this study is to further elucidate the behavior of fusariosis in humans.

Methods: We analyzed all reports of Fusarium infection in the English and German literature from 1958 to 2007. Data about the age, gender, underlying condition, symptoms, Fusarium species, treatment and outcome were analyzed.

Results: 213 cases with either histologically or culture proven infection were included. 62.5% (n=133) were male. The median age of the patients was 39.9 years (range: 0.04-82 years). The overall mortality rate was 34.7% (n=74), with a direct correlation between the underlying condition, the immune status of the patient and the site of infection. No underlying condition was found in only 4.2% (n=9) of all cases. All of them survived and none of them had a disseminated disease. A disseminated infection was detected in 40% (n=86) of all analyzed cases with fusariosis. The second leading site of Fusarium infection was the skin 22.5% (n=48) and eye 15% (n=33). *Fusarium solani* was the most frequent species. 92.5% (n=197) of all patients received antifungal therapy. The most frequent used antifungal agent

was amphotericin B deoxycholate and its liposomal equivalent. Only 6 patients received no treatment at all, neither surgery nor any sort of medication. 4 of them died.

Conclusion: From the first case in 1958 an increasing number of cases were published each decade with a peak between 1990-1999. The outcome depends on the site of infection and the immune status of the patient. Disseminated Fusariosis in immunocompromised patients had a very poor outcome. Usually a recovery is achieved as soon as the immune status of the patient improves.

2. Introduction

The mold Fusarium is a common soil saprophyte, and it is worldwide distributed in plants, soil and water (49, 53, 57, 92). Fusarium species were also detected in the hospital water systems and outdoor air (94). Fusarium species are important plant pathogens. Fusarium infections in humans are rare and used to be mostly associated with superficial mycosis (53). However, locally invasive and systemic infections are observed with increasing frequency in immunocompromised patients and have recently emerged as opportunistic fungal infections among these patients (53, 94). With the widespread use of cytoreductive and immunosuppressive therapy in patients with hematological malignancies, Fusariosis has recently become an emerging disease in immunocompromised patients (8, 9, 24, 50, 87, 94).
Fusarium species is a fungus of hyalohyphomycosis along with other fungi such as Penicillium species, or Aspergillus species.
More than 50 species of Fusarium have been described but only a few of them have been recognized as pathogenic for humans (94). The most common is *Fusarium solani* (9, 94). Followed by *Fusarium oxysporum* (2, 3, 7, 15, 23, 37, 40, 44, 54, 58, 62, 68, 83, 85, 93, 102-104, 109, 110, 113, 114, 116, 117, 121, 128, 131, 138, 140) and *Fusarium moniliforme* (28, 32, 43, 48, 63, 89, 98, 109, 136, 138, 142). Others found in the literature are *Fusarium verticilliodes* (38, 78, 105, 119, 137), *Fusarium proliferatum* (16, 59, 108, 129), *Fusarium dimerum* (12, 20, 26, 68, 71), *Fusarium chlamydosporum* (66, 125), *Fusarium roseum* (99), *Fusarium conglutinans* (76), *Fusarium*

napiforme (81), *Fusarium sacchari* (50) and *Fusarium polyphialidicum* (51). The fungus Fusarium sp. possesses several virulence factors including the production mycotoxins. These mycotoxins can suppress humoral and cellular immunity, and cause tissue breakdown. Fusarium spp. also have the ability to adhere to prosthetic material (contact lenses, catheters) (92).

The clinical manifestation of fusarosis correlates directly with the immune status of the patient and the portal of entry (94). An infection in healthy patients is rare and occurs usually only after direct inoculation or breakdown of the tissue barrier (79). It affects mostly skin and eyes (19, 53, 57). However, Fusariosis is one of the most common cause of fungal keratitis world-wide (19).

In immunocompromised patients, especially those with prolonged neutropenia the Fusarium infection often results as an invasive or disseminated disease (49). The most frequent clinical manifestation of disseminated fusariosis in these patients is refractory fever despite antibacterial and antifungal therapy with typical cutaneous lesions and positive blood culture (49, 79, 87, 94).

Due to this fact and the knowledge of the increasing number of immunosuppressed patient the aim of this study is to further elucidate the pattern of the Fusarium infection. We reviewed the English and German language literature for all cases of fusariosis, from the original case report in 1958 to 2007. In this review, we sought to understand the pattern of the infection, whether the infection is associated with specific host factors, the portal of entry, treatment and outcome.

3. Methods

We conducted a systematic literature search of the MEDLINE, to identify all reported cases with an infection due to Fusarium sp. After the initial search we scanned the references listed on each publication to gain additional cases. Only cases with either histologically or culture proven Fusarium infection were included. Data about the anatomical location of the infection, risk factors (e.g. immunosuppression, antibiotic treatment, steroids, and injury), age and gender of the patient, treatment and outcome were collected and analyzed.

A disseminated infection was defined as an infection at two or more noncontiguous sites.

4. Results

213 cases of fusariosis were included in our analysis. In 1958, the first case of Fusarium infection was mentioned in a patient after an eye injury due to a cowtail (83). The inflamed eye was treated with antibiotics and steroids without improvement. Pus in the anterior chamber and a perforated ulcer developed. A smear finally proved a Fusarium infection. The eye had to be enucleated in order to achieve a complete recovery from the infection. From this first case of Fusarium infection an increasing number of cases were published in the literature in each decade, reaching a peak between 1990-1999 (figure 1).

Demographic characteristics

The median age of all patients was 38.95 years with a range from 0.04-82 years. 72 patients (33.8%) were over the age of 50 years, 26 patients (12.2%) under the age of 10 years. A total of 62.4% (n=133) of all Fusarium infections occurred in males, 35.2% (n= 75) in females. In 2% (n=5) of all cases the gender of the patient was not mentioned at all.

The overall mortality rate was 34.7% (74 of 213 Patients did not survive the infection), 49.7% (n=106) achieved a complete recovery. In the remaining 15.6% (n=33) there was either a stable disease or the patient was lost to follow-up.

The most common underlying condition and major risk factor to become infected from a Fusarium sp. was any antibiotic treatment (63.9%), followed by hematologic malignancies (44.1%). Predisposing job or hobbies, such as farming or gardening were found in 6.1% of the cases. However, 77.4% (n=164) of all patients had more than just one risk factor. No underlying condition was found in only 9 cases (4.2%). All 9 cases had a localized infection and survived (table 1).

Change of Fusarium infections during study period

In 1950-1959 trauma was the most common underlying condition. After 1960 the leading underlying condition in each decade was any use of antibiotics. Hematologic malignancies were not known as underlying condition until 1970. After 1980 it became the second most underlying condition with a peak in 1990-1999 (figure 1). However, over all decades the hematologic malignancies with consecutive chemotherapy and neutropenia, which requires the broad use of antibiotics, are the most important risk factors of Fusarium infections.

Besides the medical progress with its associated ICU treatments, foreign devices in the body, such as catheters and grafts are frequently associated with Fusarium infections.

Sites of infection

Fusarium infection can be superficial, locally invasive or disseminated. The site of infection depends mainly on the underlying condition and correlates directly with the immune status of the patient and the site of entry (table 1).

A disseminated infection was diagnosed in 74.4% (n=64) of all cases associated with a hematologic malignancy. Chemotherapy and neutropenia are also important risk factors to develop a disseminated infection (65.1% of all cases, n=56 in both cases).

In 69.6% (n=23) of all eye infections there was a prior antibiotic treatment. The second underlying risk factor for eye infections was the use of local steroids (51.5%, n=17), followed by foreign devices in the eye such as contact lenses (42.4%, n=14) and trauma (36.3%, n=12).

Regarding the skin infection, the most common risk factor was also the use of antibiotics (47.9%, n=23), followed by hematologic malignancies (39.6%, n=19), chemotherapy (35.4%, n=17) and neutropenia (29.1%, n=14).

Positive blood cultures was obviously often associated with foreign devices, such as catheters and grafts (81.9%, n=9).

In most cases of nail infections no underlying condition could be found (71.5%).

Bone infections were often associated with diabetes mellitus (50%),

All patients with Fusarium endocarditis had an intravascular catheter.

The two cases with peritonitis were both associated with peritoneal dialysis.

Clinical manifestation

The clinical manifestation depended on the site of infection.
The most frequent clinical manifestation in patients with disseminated fusariosis was refractory fever. Further typical cutaneous lesions were mentioned in 44% of all disseminated cases. Skin lesions presented themselves as erythematous painful cutaneous or subcutaneous papular nodules.
Pulmonary infiltrations were found in 23% of the cases with disseminated fusariosis. An eye infection usually presents itself by decreasing vision and painful watery injected eyes, later with corneal ulcer. In nail infection a yellow or white discoloration periungular was seen.

Microbiological findings

The most common species was *F. solani* in 34.3%, followed by *F. oxysporum* in 17.8%, *F. moniliforme* 5.6%. Only sporadic infections with *F. verticilloides, F. proliferatum, F. dimerum F. roseum, F. chlamydosporum, F. conglutinans, F. polyphialdicum, F. napiforme, F. sachari* were reported (table 1). In 26.4% (n=63) the exact species was not documented. *F. solani* seems to be the most virulent species. 34.9% (n=25) of all disseminated infections are caused by *F. solani* and 30.1% (n=22) of all patients with *F. solani* infection died. *F. oxysporum* was in 17.4% (n=15) associated with a disseminated disease, *F. moniliforme* and *F. verticilliodes* in 5.8% (n=5). *F. proliferatum* and *F. dimerum* were only found in 3 patents with disseminated disease.

Figure 1: Number of patients mentioned in the literature with Fusarium infection per decade.

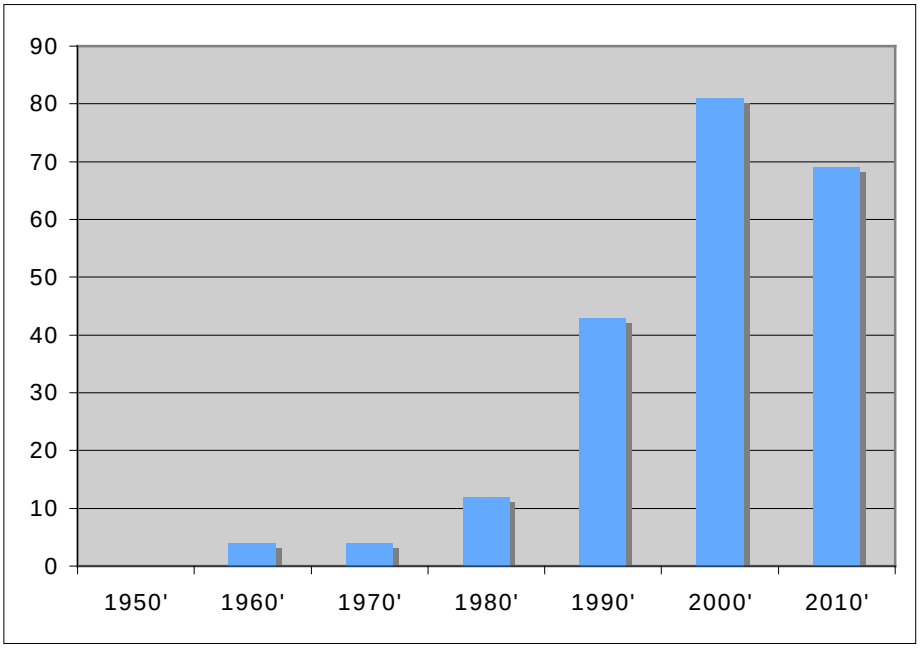


Table 1: Demographic and clinical characteristics

Characteristic	No. of patients	No. of patients who died
Total	213	74/213 (34.7%)
Age		
• mean	38.95	
• range	0.04-82	
Sex		
• male	133 (62.4%)	
• female	75 (35.2%)	
• unknown	5 (2.4%)	
Underlying condition		
• Medication		
- steroids	31 (14.6%)	9 (29%)
- antibiotics	136 (63.9%)	56 (41.2%)
• Tumor		
- solid organ	15 (7%)	7 (46.7%)
- hematologic	94 (44.1%)	46 (48.9%)
• Transplantation		
- kidney	3 (1.4%)	2 (66.7%)
- liver	1 (0.5%)	0
- heart/liver	1 (0.5%)	0
- lung	3 (1.4%)	2 (66.7%)
- bone marrow	27 (12.7%)	20 (74.0%)
• Trauma/burns	34 (16%)	3 (8.8%)
• Foreign body		
- catheter	25 (11.7%)	11 (44%)
- contact lens	15 (7%)	0
- graft	3 (1.4%)	3 (100%)
- nasogastric tube	2 (0.9%)	0
- dialysis	3 (1.4%)	0
• no	9 (4.2%)	0
Site of infection		
• disseminated	86 (40.4%)	50 (58.1%)
• skin	48 (22.5%)	12 (25%)
• eye	33 (15.5%)	0 (0%)
• ORL	10 (4.7%)	4 (40%)
• blood	11 (5.2%)	1 (9.1%)
• nail	8 (3.8%)	0
• bone	6 (2.8%)	0
• joint	3 (1.4%)	1 (33.3%)
• lung	3 (1.4%)	1 (33.3%)
• endocarditis	3 (1.4%)	3 (100%)
• peritoneum	2 (0.9%)	0 (0%)
Species		
• *F. solani*	73 (34.3%)	22 (30.1%)
• *Species unknown*	63 (29.6%)	22 (34.9%)
• *F. oxysporum*	38 (17.8%)	14 (36.8%)
• *F. moniliforme*	12 (5.6%)	6 (50%)
• *F. verticilliodes*	7 (3.3%)	3 (42.9%)
• *F. proliferatum*	7 (3.3%)	2 (28.6%)
• *F. dimerum*	5 (2.4%)	3 (60%)
• *F. roseum*	2 (0.9%)	0 (0%)
• *F. chlamydosporum*	2 (0.9%)	1 (50%)
• *F. conglutinans*	1 (0.5%)	0
• *F. polyphialidicum*	1 (0.5%)	0
• *F. napiforme*	1 (0.5%)	0
	1 (0.5%)	0

Treatment

The treatment depended on the site of infection. 197 (92.5%) of the reviewed 213 cases were treated with any antifungal therapy. Most of the patients received a combination of different antifungal pharmaceuticals. Only 6 patients (3 with disseminated, 1 with burns and 2 with skin infection) received no treatment at all, 4 of them died, among them the 2 cases with disseminated infections and the one with burns. In 3 of these cases the diagnosis of Fusarium infection was made post mortem.

Surgery alone was used in 7 patients with superficial infection. All of them survived.

The most widely used antifungal therapy was amphotericin B deoxycholate (62.5%,n=133) with its first use in 1964. The second most used was liposomal amphotericin B (17.5%, n=37), first administered in 1991. Followed by flucytosin (n=30), fluconazole (11.3%, n=24), voriconazole (12.2%, n=26), itraconazole (9.4%, n=20), ketokonazole (8.5%, n=18) and rifampicin (7.0%, n=15). Besides the antifungal therapy and surgery the use of Granulocyte transfusions and G-CSF transfusion was used.

Between 1958-1959 none of the above mentioned antifungal therapy was known. Surgery was the treatment of choice. Later on, between 1960-1969 the first antifungal therapy came in place. For a long time amphotericin B deoxycholate was the only known antifungal pharmaceutical, until 1979 when flucytosin came in place, followed by ketokonazole (1986). The first use of G-CSF was mentioned in 1990.

In 1991 the first use of liposomal amphotericin B was reported, 1992 the first use of fluconazole, 1994 itraconazole and 2003 voriconazole. Many patients (27.2%, n=58) received a combination of antifungal agents. Rifampicin was never used as a single drug, but always in combination with an antifungal agent, most often with amphotericin B. In 56 of the 58 cases with a combination antifungal therapy, amphotericin B was one component of the combination. In the later decades voriconazole was widely used in a combination therapy. The most frequently used combination was amphotericin B/flucytosin (9.4%, n=20), followed by amphotericin B/voriconazole (3.8%, n=8), amphotericin B/rifampicin (3.3%, n=7) and amphotericin B/ketoconazole (1.9%, n=4). Other combinations used where amphotericin B/fluconazole in 3 cases, amphotericin B/itraconazole in 2 cases and ketoconazole/rifampicin in 1 case.

Triple combinations were used in 12 cases:

- amphotericin B/flucytosin/rifampicin (n=2)
- rifampicin/ketoconazole/amphotericin B (n=2)
- amphotericin B/flucytosin/ketoconacole (n=2)
- amphotericin B/voriconazole/fluconazole (n=2)
- amphotericin B/fluconazole/itraconazole (n=1)
- amphotericin B/voriconazole/itraconazole (n=1)
- amphotericin B/flucytosin/itraconazole (n=1)
- amphotericin B/fluconazole/rifampicin (n=1)

The use of voriconazole in combination with another antifungal drug seems to be a successful treatment with a recovery rate of 90%. On the other hand rifampicin in combination with an antifungal agent seems to be a poor choice: 69.2% of the patients didn’t survive the infection. 53.5% of the patient who received a combination therapy survived.

Table 2: Treatment administered to 213 patients with fusariosis

Treatment	**No. of patients**	**No. of patients who died**
Amphotericin B		
- deoxycholate	133 (17.5%)	56 (42.1%)
- lipid/liposomal	37 (17.5%)	12 (32.4%)
Flucytosin	30 (14.1%)	17 (20.3%)
Fluconazole	24 (11.3%)	11 (45.8%)
Voriconazole	26 (12.2%)	1 (3.8%)
Itraconazole	20 (9.4%)	6 (30%)
Ketoconazole	18 (8.5%)	5 (27.8%)
Rifampicin	13 (6.1%)	9 (69.2%)
Surgery	75 (35.2%)	13 (17.3%)
G-Transfusion	12 (5.7%)	6 (50%)
G-CSF	25 (11.8%)	12 (42.9%)
No therapy	6 (2.9%)	4 (33.3%)

Outcome

The overall mortality was 34.7% (n=74). A complete recovery was achieved in 49.7%. 15.5% of the patients were lost to follow-up was. The mortality rate was strongly associated with the underlying condition and the site of infection. A disseminated infection is obviously associated with a worse outcome. 58.1% of all patients with disseminated infections died, whereas only in 36.0% a complete recovery was achieved. A disseminated fusariosis was only seen in immonocompromised patients.

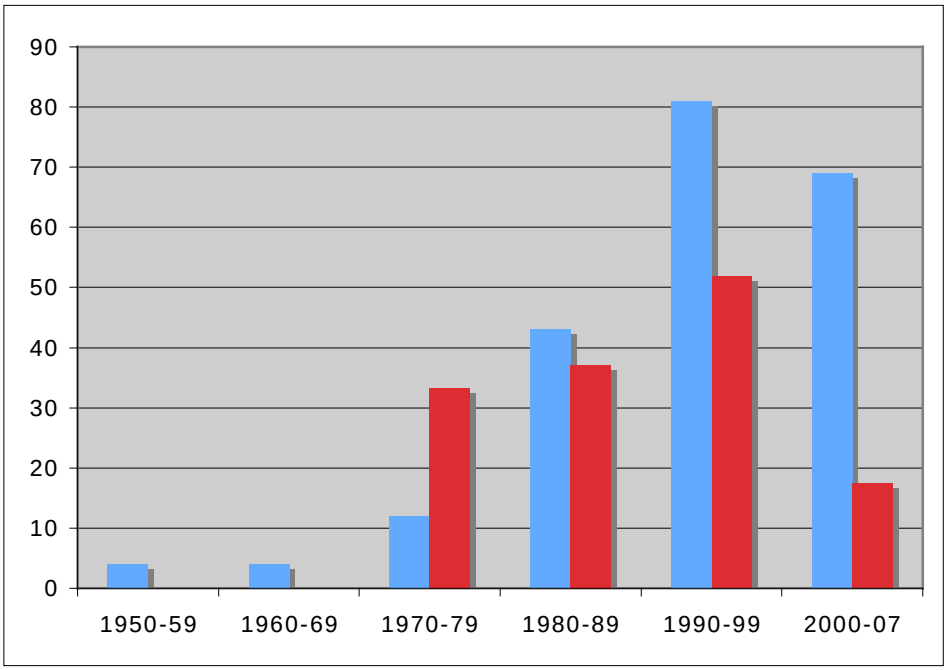
All 3 patients with a Fusarium endocarditis didn't survive. 25% of the patient with a skin Fusarium infection died. An eye infection leaded never to death.

An underlying hematologic malignancy was the most important risk factor for death. 48.9% (n=46) of all patients with hematologic malignancies didn't survive the infection.

All patients with no underlying condition survived the infection.

Regarding the mortality rate per decade there is a notable increase in the mortality rate each decade, reaching a peak in the 1990-1999 with 51.9% patients with fusariosis dying (figure 2). This trend was attributed to the widespread and, immunosuppressive therapy and increasing use of antibiotics. Finally a decrease of the death rate was recognizable in the time of 2000-2007 with a mortality rate of 16.4% (12 of 69 patients). In most cases it was seen that as soon as the patients achieves a recovery of its own body defense, he will recover from the infection.

Figure 2: number of patients (light) and death rate in % (dark) compared to decade



5. Discussion

Fusariosis is an emerging disease, especially in immonocompromised patients. *Fusarium spp.* causes a broad spectrum of infections in humans, including superficial, locally invasive, and disseminated infections (94). To our knowledge, this is the first study including all published Fusarium infections. The first reported case of a Fusarium infection was in 1958 (83). Unlike other known filamentous fungal pathogens, Fusarium affects mostly immunocompromised hosts. Our study showed that, in contrast to other mold infections, such as zygomycetes (112), diabetes or solid tumors don't seem to be important risk factors to get infected with *Fusarium ssp*.. Only a few cases, namely 10 were found in patients with solid tumor. Only 4 cases were observed in patients with diabetes mellitus as a risk factor. All of them had a localized infection, either a skin infection or an infection in the otorhinolaryngological site. Each one achieved full recovery. No underlying condition was found in 9 cases at all.

The most important risk factor for severe fusariosis is prolonged neutropenia in patients suffering from a hematologic malignancy, including especially hematopoietic stem cell transplantions. Fusarium infection is in the vast majority of the cases caused by a breakdown of the human defense. Either by trauma with affects the natural skin defense, or in immunocompromised hosts. Fusariosis is rare in a healthy person and occurs usually only after direct inoculation or tissue breakdown (as caused by trauma, severe burns

or foreign body). No disseminated infection was found in healthy people. However, infections include keratitis, onychomycosis and occasionally peritonitis and cellulitis. Treatment is usually successful and requires surgery, removal of a possible foreign body as well as antifungal therapy.

In disseminated fusariosis refractory fever and cuatenous lesions are the most important symptoms. Type of skin lesions includes ecthyma-like, target, and multiple subcutaneous nodules. Skin lesions lead to diagnosis in > 50% of patients and precede fungemia by approximately 5 days. In contrast to aspergillosis, fusariosis frequently shows positive blood cultures. This is because *Fusarium spp.* sporulate, which facilitates bloodborne disseminated growth (13).

The culture methods typically have a low sensitivity for identifying the Fusarium species. Species identification may be difficult and may require the use of molecular techniques. PCR methods are available but the identification is complex and requires a highly skilled laboratory staff (27). The use of mass spectrometry to identify the *Fusarium ssp.* has recently gained popularity (27). Matrix-assisted laser desorption ionization-time of light (MALDI-TOF) is a tool that has been used to characterize fungi (27, 31, 132). But so far there is no standard protocol or validated database to use the MALDI-TOF in a routine lab (27). The most common species found in our study was *F. solani*, followed by *F. oxysporum*, *F. moniliforme*, *F. verticilloides*, *F. proliferatum* and *F. dimerum*. In our study, *F. solani* seemed to be the most virulent species with the highest mortality rate.

Optimal treatment has not been established, yet. Anecdotal successes have been reported with various agents (high-dose amphotericin B, lipid-based amphotericin B formulations, itraconazole, voriconazole) and with cytokine-stimulated granulocyte transfusions. A study of Astor et al. (13) analyzed the susceptibility of the different *Fusarium ssp*. to antifungals in vitro. The result showed that terbinafine was most effective, followed by voriconzole and amphotericin B. In our study terbinafine was not used in the treatment of fusariosis. However, Combinationtherapies containing voriconazole showed a favorable outcome. Further studies should be conducted addressing the terbinafine in combination with voriconazole in treatment of an infection due to *Fusarium spp*.

Given the poor prognosis associated with disseminated fusariosis in immunocompromised patients, prevention is the cornerstone of management (94). The high risk patients have to be in rooms with HEPA filters. Further, contact with reservoirs of *Fusarium spp.* such as food or tap water should be avoided.
In conclusion, infections by *Fusarium spp.* can be superficial or limited to single organs in non immunocompromised host. Such infections are rare and tend to respond well to therapy. By contrast, disseminated fusariosis occurs in the immunocompromised host, especially in hemato-oncological patients with severe and prolonged neutropenia. These patients die frequently in this setting, and successful outcome is determined largely by the degree and persistence of immunosuppression. Fusariosis may be clinically

suspected on the basis of the clinical presentation and laboratory findings. A prompt therapy should be started.

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7. Curriculum vitae

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